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Chapter 5

Principles of Cancer Immunobiology and Immunotherapy of Solid Tumors

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/61211

Abstract

The immune system and cancer coexist in close relationship which is an indispensable part of the processes of tumorigenesis, tumor growth, and metastatic spread. The elucidation and understanding of this continuous process could provide opportunities to develop strategies to impact the prognosis, and eventually to improve the cancer treatment process. Such strategies have been already implicated and proven efficient in the treatment of several tumor localizations such as malignant melanoma, lung and renal cancer. The present publication reviews the principles of cancer-related immune response, types and mechanisms of immune response and suppression, immunotherapy of solid tumors. We also discuss the pathways and the signaling molecules, participating in those immune response/suppression processes, turning them into potential targets and their actual and potential future role in the management of solid tumors. We focus on potential role and rationale for combination of immunotherapeutic and chemotherapeutic/targeted agents and radiotherapy in one treatment strategy.

Keywords: immune response, immune suppression, checkpoint inhibitors, immunotherapy, solid tumors

1. Introduction

The relationship between the immune system and cancer has recently become a "modern topic" of interest in cancer research even though it was back in the early 1800s, when Virchow first described the presence of inflammatory cells in pathohistological tumor samples. Subsequently, Coley demonstrated that the use of bacterial products induced certain regression in inoperable tumors [1]. It has been known for decades that the immune system plays an important role in the processes of inflammation, chronic inflammation, and cancer. Thus,

scientific researchers continued the struggle to understand the role of Virchow's findings, aiming to link those processes. The elucidation of such relation could give an insight into the processes of tumorigenesis, tumor growth, and metastatic spread; it could potentially provide subsequent opportunities to develop strategies to impact the diagnosis, prognosis, and eventually to improve the cancer treatment process. The synallagmatic reciprocal talk between the host immune system and the tumor has been intensively studied. The processes of the host immune control over the tumor, immunoediting by the tumor, the immune escape, and the development of immune tolerance and suppression are described in this chapter. Our aim is also 1) to highlight the principles of cancer-related immune mechanisms, immunotherapy, and their role in the process of treatment of solid tumors; - and 2) to discuss the options to combine immunotherapeutic and chemotherapeutic agents trying to overcome the mechanisms of immune or inflammatory suppression and potentially improve cancer treatment strategies.

The initial immune-related therapies were aiming to activate the immune system and were represented by non-specific immunotherapies that didn't aim towards a specific target in the cancer cell (cytokines, interleukins, interferons, etc.). Subsequent efforts tried to identify antigens of the cancer cell and to design monoclonal antibodies (MAB), targeting those antigens. However, it has become clear that these therapies are failing because of the ability of cancers to induce immune tolerance, evasion, and suppression of the immune system, which created a new direction of research - to discover the pathways and the signaling molecules, participating in those immune suppression processes, thus turning them into potential targets as anticancer treatments.

2. Basic principles of immune response

There has been major growth in the understanding of the immune role and its relationship to cancer progression and therapy. The immune system comprises of a multitude of interconnected cells and tissues, distributed in the body. It basically consists of three general categories of blood cells: 1) lymphocytes (T, B cells and natural killer (NK) cells); 2) myeloid cells (macrophages, dendritic cells, and antigen presenting cells); and 3) granulocytes (neutrophils, basophils, and eosinophils). Simplified, the immune system protects the organism from harmful foreign agents (antigens) by producing specific proteins (antibodies). Those antibodies circulate until they find and attach to the targeted antigen, thus triggering immune response and destruction of the antigen-containing cells.

2.1. Principles of immune response in solid tumors

The anti-cancer immune response could be largely divided into two types: innate and adaptive immune response. The innate immunity includes the granulocytes, macrophages, dendritic cells, mast cells, and NK cells serving as a first-line protective mechanism, recognizing stressed mutating cells of the organism, and triggering effector mechanism, aiming their eradication. Subsequently, the adaptive immune response is triggered - it consists of specific immune activation of B cells, CD 4- and CD 8-expressing T-lymphocytes.

http://dx.doi.org/10.5772/61211

2.1.1. Innate antitumor response

Normal cells of the organism could become subject of malignant genetic and epigenetic transformation and thus acquire additional characteristics, permitting their uncontrolled proliferation, survival, and dissemination. Such genetic injuries stimulate the innate immune system, which normally serves as a front-line surveillance mechanism, reacting immediately. The NK cells distinguish normal from tumor cells by a complex process of expression of different inhibitory and stimulatory molecules. Specific MHC inhibitory receptors have been described, shedding light over the molecular basis of the activation of the NK cell during the process of natural cytotoxicity of the innate antitumor response. Different receptors frequently referred to as natural cytotoxicity receptors (NCR) are expressed at the surface of the NK cell; they comprise of molecules such as NKp46, NKp30, NKp44, and NKG2D, which bind to their ligands of the MHC class I [2]. NKG2D appears to play either a complementary or a synergistic role with NCRs. The expression of those ligands is induced on the surface of the stressed transformed tumor cells [3,4]. The binding of the MHC-I related ligands to the NKG2D triggers activation of NK cells, NKT and γδ T cells, and CD 8 T cells, which inhibit tumor cytotoxicity and IFN-γ production. Extracellular release of cytoplasmic stress molecules, such as HSP-70, HMGB1, and uric acid, activates macrophages and dendritic cells, resulting in IL-12 production and transition to the adaptive immunity [5].

2.1.2. Adaptive antitumor responses

The adaptive immune response could be described as the "second-line" response. As a highly specific response to a specific pathogen, it starts relatively later after the initial rapid innate reaction. It is triggered by the dendritic cells, which capture, process, and present tumor antigens to the class I and II MHC, thus stimulating the antigen-specific T- and B-lymphocytes (cellular response) and the specific production of antibodies (humoral component).

Macrophages, dendritic cells, and antigen-presenting cells (APCs) recognize foreign cells and participate in the immune response as they are one of the first responders, approaching a potential harmful antigen. They internalize those extracellular antigens via phagocytosis or receptor-mediated endocytosis; they process and fragment the proteins into peptide sequences that are subsequently presented back at the extracellular membrane surface of the APCs within the context of the Major Histocompatibility Complex (MHC) class II (Figure 1). They also produce large amounts of different cytokines, thus promoting immune response. In cases of inadequately directed immune reaction towards self-antigens, the dendritic cells particularly prevent further autoimmune reaction [6]. In order to prevent self-destruction, the immune system uses endogenous crosstalks—"immune checkpoints"—that normally terminate immune responses after antigens activation of T-cells.

Once the immune response is triggered, the foreign antigen is presented to other cells of the immune complex. More specialized cells, the lymphocytes, encounter the foreign antigen and respond by proliferation and differentiation into different subpopulations. B-lymphocytes arise and differentiate in the bone marrow and enter into the blood stream as functional mature cells. They express a receptor for the antigen on their surface and following encounter with that specific antigen, they start to divide, differentiate into plasma cells, and produce soluble

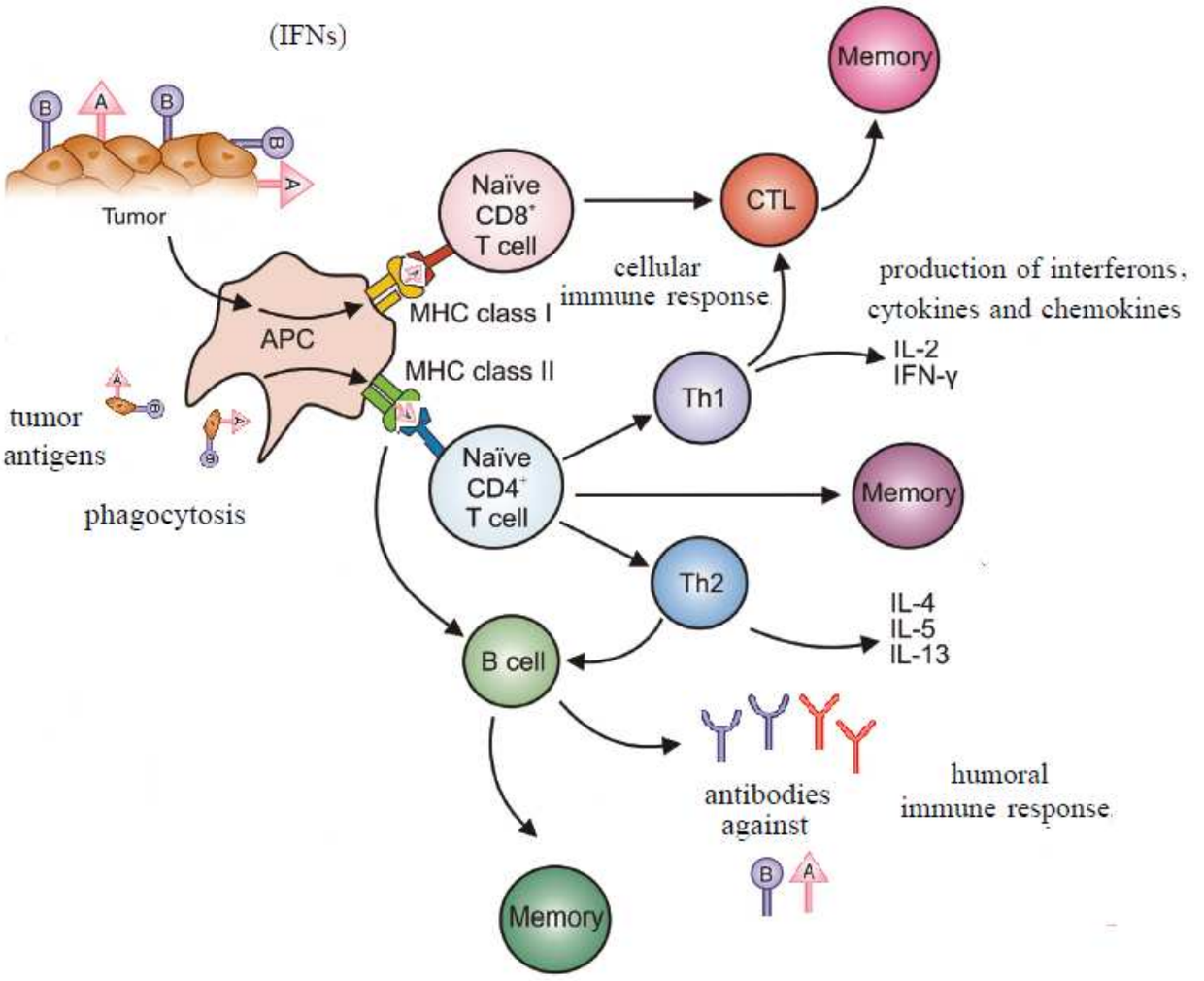

Figure 1. Induction of rapid innate and retarded adaptive immune response (humoral and cellular T- and B-cell response). Tumor cell proteins are degraded into smaller peptides in endosomes/lysosomes in the APCs and are subsequently expressed on the cell surface in MHC class II peptide complexes, which can be recognized by CD4+ T helper lymphocyte cells. T helpers assist B cells to proliferate and mature into antibody-producing plasma cells. Via this route of antigen acquisition, DCs can also present epitopes to CD8+ T cells. This is also known as cross-presentation.

immunoglobulin molecules—antibodies in the circulation. T cells arise in the bone marrow and migrate to the thymus (named thereafter) where they undergo a process of maturation. Immunocompetent T cells leave the thymus and enter into the circulation. There are different T cells classified by their function and phenotype. The largest part of T cells expresses CD 4 glycoprotein and are called T helpers. They enhance the immune process by secreting cytokines and direct cell-to-cell contact [7]. Other numerous specific functional T-lymphocytes are called cytotoxic (CTLs). They express CD8 glycoprotein and are capable of direct killing of the antigen-containing cells (virally infected or cancerous). Upon encounter of their target, they kill it by induction of apoptosis in the infected or cancerous cell. A part of the lymphocytes remain as sensitized long-living memory cells, recognizing only a single antigen, posed to respond if it is encountered again. The regulatory T cells (T regs) are a small population of T cells and express CD 25 glycoprotein, which participate in the process of self-antigen recog-

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nition, preventing autoimmune reactions [8, 9]. If the immune system functions correctly, its work remains unnoticed, efficiently protecting the individual from a variety of foreign pathogens. In cases of dysfunction, however, severe consequences appear, presented either as immunodeficiency or autoimmunity.

3. Principles of cancer immunobiology: Immunoediting, surveillance, and immune escape

The importance of intact immune surveillance in controlling the outgrowth of neoplastic transformation has been known for decades [10]. With the discovery of the cellular oncogenes, it became evident that human cancers arise from normal cells and harbor various genetic and epigenetic alterations, generating potentially recognizable by the immune system cancer neoantigens [11]. Being of host origin, cancer cells share features of the host. The plastic nature of tumors makes them adaptive in rebounding from clinical regimens of radiotherapy/chemotherapy that are traditionally used. The tumor progression can be described as a continuum of multiple clonal expansions, each of which triggered by the fortunate acquisition of an enabling mutant genotype. Even when the vast majority of cancer cells are killed by a cytotoxic chemotherapy drug, a small number of residual cells are primarily or become secondarily resistant to that agent. They can be sufficient enough to seed the subsequent tumor regrowth that is resistant to the previously used chemotherapy agent. This leads to the concept of selection of tumor cells and evolving resistance that becomes a key disease progression feature; development and progression of cancer is driven by the selection of cells that survive conditions that are normally lethal. Resistance to any normally lethal condition (radiotherapy, chemotherapy, etc.) can be selected by the cancer cell population evolution because of the genetic plasticity, which is an important feature of the cancer cell [12].

The tumor development is a multi-step process, requiring the acquisition of several biological features: 1) sustained proliferation signaling; 2) evasion of growth suppression; 3) apoptosis escape; 4) uncontrolled growth and reproduction; 5) angiogenesis induction; and 6) invasion and metastasizing potential. These hallmarks of the tumor cells ensure their survival, proliferation, and dissemination [13]. There are other characteristics that facilitate the acquisition of these hallmarks by the cancer cells, such as the tumor-associated stromal microenvironment and inflammation, genomic instability, and mutations, mediating the process of tumorigenesis [14]. There are two more features that are functionally important for the development of cancer hallmarks. The first feature involves major reprogramming and deregulation of cellular energy metabolism in order to continuously ensure cell growth and proliferation. The second feature involves active tumor escape of the immune system destruction and elimination. This capability highlights the dichotomous role of the immune system that both suppresses and enhances cancer initiation, promotion, and progression [15-17]. Both of these features may well prove to facilitate the initiation and progression of many forms of malignant human solid tumors [14].

There is a theory suggesting that cells and tissues are constantly monitored by an ever-alert immune system, and that such immune surveillance is responsible for recognizing and eliminating the vast majority of incipient cancer cells and thus nascent tumors. According to this logic, solid tumors that do appear have somehow managed to avoid detection by the immune system or have been able to limit the extent of immunological killing, thereby escaping eradication. This is a process called immunoediting—a tumor mechanism, exerting an extrinsic suppression; it occurs only after a malignant cancerous transformation has already occurred and the intrinsic tumor suppressor mechanisms have already failed. The cancer immunoediting roughly consists of three sequential phases: elimination, equilibrium, and escape. In the first phase, the body immune system successfully detects cancer cells and eliminates them efficiently [18,19]. In the equilibrium phase the immune system obstructs tumor growth, but is unable to completely eradicate the tumor. This step is thought to be continuous in time and it could either progress to the last escape phase or reverse backwards, leading to complete tumor eradication by the immune system. If this second phase continues for a longer period of time, the immune system is incapable of tumor eradication and continuously interacts with the tumor, thus sculpturing or editing the tumor genetics [20-22]. In the last phase, the tumor growth is no longer controlled and blocked by the immune system and the tumor spreads and produces clinically apparent diseases [23].

4. Targets and types of immunotherapy in solid tumors

Immunotherapy is defined as an interaction with the immune system aiming to treat/cure cancer. Immunotherapy could be largely divided into passive and active.

4.1. Active immunotherapy

Active immunotherapy has recently undergone active clinical research. As tumors express multiple tumor-associated antigens or neonatigens, the immune system should respond by adaptive activation of T-lymphocytes against those potential targets as previously described in section 3.1.2. Any mechanism leading to activation of the immune system is considered as active immunotherapy. Active immunotherapy has been developed in order to induce and stimulate the individual's own immune response. An example of this still-developing branch of immunotherapy represents Sipuleucel-T, which is the first active cellular immunotherapy approved for clinical use by the American Food and Drug Agency (FDA) in the treatment of prostate cancer based on the data that a benefit in survival was observed in the group of asymptomatic or minimally symptomatic patients with Castrate-resistant prostate cancer (CRPC) [24]. It consists of autologous peripheral-blood mononuclear cells obtained by leucopheresis, cultured and activated ex vivo with a recombinant human fusion protein PA2024 consisting of prostatic acid phosphatase linked to granulocyte-macrophage colony-stimulating factor (PAP-GM-CSF). GM-CSF stimulates the maturation process of APCs to mature DCs, while PAP peptides functions with MHC I and II. Upon reinfusion in the patient, an immune response against PAP-containing cells is triggered [24,25].

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Another example of active immunotherapy is the cellular adoptive immunotherapy using transfusion of the patient's own T-lymphocytes previously stimulated ex vivo and currently tested in phase I/II trials. There is also a wealth of trials with autologous or donor dendritic cells, autologous tumor cell lysate, activated lymphocytes, or vaccines (DNA, peptide, recombinant viral vector vaccines, etc.) used as monotherapy or in combination with chemotherapy or other passive immunotherapy options such as anti-CTLA 4 MAB, anti-PD-1 MAB, and anti-PD-L1 MAB [26-30].

4.2. Passive immunotherapy

At present, passive immunotherapy is still more commonly used as it refers to the delivery of previously synthesized agents that could be used by the immune system; typical examples are the use of non-specific immunomodulatory cytokines IFN-α, IL-2, or the specific MAB. Early clinical studies demonstrated that the use of immunomodulatory cytokines such as interferon alpha (IFN α) or interleukin 2 (IL-2) may induce antitumor immune-mediated effects as tumor regression in some solid malignancies [31,32]. Cytokines have been used as cancer immunotherapy for long decades and they work either by exerting a direct antitumor effect or by indirectly enhancing the antitumor immune response [33]. Multiple in vitro studies have shown that TNF-α and IL-6 exert direct antitumor effect suppressing cancer cell growth and survival. However, clinical use of these cytokines in cancer patients has led to less successful results because of significant toxicity and the controversial influence of a single molecule such as TNF-α and IL-6. Although they are able to suppress tumor growth, they actually promote growth of other tumors; further on, IL-6 may also exert immunosuppression. Therefore, the use of the direct antitumor effect of cytokines remains exclusively an academic pursuit.

In contrast, other cytokines may enhance the antitumor immune response through a variety of different pathways and thus they are more widely used in the clinical practice. For example, IL-2 and IFN-α promote T-lymphocytes and NK cells growth and activation, while granulocyte-macrophage colony-stimulating factor (GM-CSF) acts on APCs, increasing the processes of antigen processing and presentation as well as the production of co-stimulatory cytokines. These cytokines are nowadays well-established cancer immunotherapies, e.g., IL-2 is used in the treatment of metastatic melanoma and metastatic renal cell carcinoma, and IFN-α is approved for the treatment of malignant melanoma [34,35]. There are reports in the literature where recombinant IL-2 has also been used in the treatment of other solid tumor malignancies, including neuroendocrine tumors [36]. This led to the introduction of immunotherapy as an anticancer treatment for metastatic renal cell carcinoma in 1992 and metastatic melanoma in 1998. Subsequently, immunotherapy with interferon was also approved in the adjuvant setting in patients with high-risk malignant melanoma as it was considered a beneficial approach [37,38]. Some other cytokines, such as IL-7, IL-11, IL-12, IL-15, IL-21, IFN-β, and IFN-γ, are also currently evaluated as cancer immunotherapies.

Another typical example of passive immunotherapy is the use of MAB. There are multiple MAB used in the treatment of solid malignancies such as the MAB against the Epidermal Growth Factor (EGFR antibody) *cetuximab* or the antibody targeting the Human Epidermal Receptor type 2 (HER 2) *trastuzumab*. These MAB specifically target their receptor at the cancer

cell surface and by binding to it, they prevent the signal cascade, transmitted intracellularly, thus preventing further tumor growth or reproduction. MAB may also target soluble circulatory factors that are important for the tumor such as the MAB *bevacizumab*, which targets the vascular endothelial growth factor (VEGF).

MAB may target not only tumor pathways. More recent research focused on the "communication" between the host and the tumor, targeting the immune system as a mechanism and controlling this process. The PD-1/PD-L1 interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1 under healthy conditions is to downmodulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 is expressed by activated T cells, mediating immunosuppression (Figure 2).

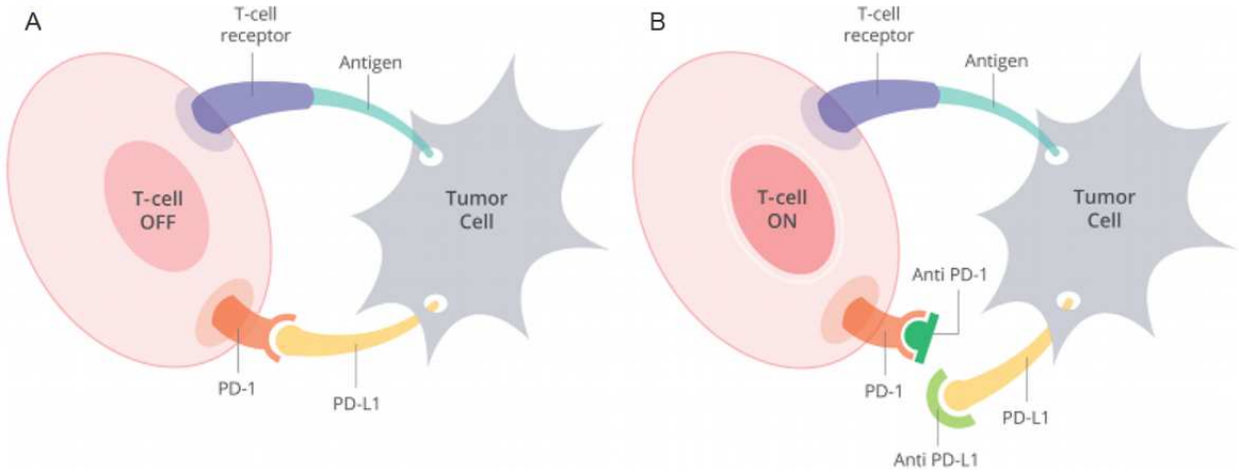

Figure 2. Immunosuppression, mediated via PD-1/PD-L1 pathway. A) PD-1 is expressed by activated T cells; by binding to PD-L1, it mediates T-lymphocyte suppression. B) The use of immune checkpoint inhibitors (anti-PD-1 or anti-PD-L1 MAB) leads to the interruption of this immunosuppression and potential cytotoxicity exerted by the T cells.

PD-1 functions in peripheral tissues where T cells encounter immunosuppressive PD-1 ligands PD-L1 and PD-L2 that are expressed by tumor cells, stromal cells, or both [39-42]. Inhibition of the interaction between PD-1 and PD-L1 enhances T cell responses in vitro and mediates preclinical antitumor activity [39,43]. PD-L1 leads to inhibition of the T-lymphocyte proliferation, survival and effector functions (cytotoxicity, cytokine release), inducing apoptosis of tumor-specific T cells, and promoting the differentiation of $CD4^+$ T cells into regulatory T cells. The blockade of PD-1/PD-L1 results in a potent and durable tumor regression and prolonged stabilization in patients with advanced malignancies [44]. Therefore, inhibition of PD-L1 binding to PD-1 represents an attractive strategy to restore tumor-specific T cell immunity.

The mechanism by which PD-1 down modulates T cell responses is similar to, but distinct from, that of CTLA-4 as both molecules regulate an overlapping set of signaling protein. PD-1 was shown to be expressed on T cells, B cells, monocytes, and natural killer T cells, following

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their activation [45,46]. PD-L1 and PD-L2 are expressed in a variety of cell types, including non-hematopoietic tissues, as well as in various malignancies. PD-L1 is expressed at low levels on non-hematopoietic tissues, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells in lymphoid tissue or chronic inflammatory environments. PD-L2 controls immune T cell activation in lymphoid organs, whereas PD-L1 serves to protect healthy tissues from unwarranted T-cell immune-mediated damage.

Although healthy organs express little (if any) PD-L1, many cancers express abundant levels of this T cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent, PD-L2) has been found to correlate with poor prognosis and survival in various cancers, including RCC [47], pancreatic carcinoma [48], hepatocellular carcinoma [49], and ovarian carcinoma [50]. Furthermore, PD-1 has been suggested to regulate tumor-specific T cell expansion in melanoma patients [51].

The observed correlation of clinical prognosis with PD-L expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Over the past several decades, these observations have resulted in intensive efforts to develop immunotherapeutic approaches as cancer treatment options. Such agents include immune-checkpoint-pathway inhibitors such as anti-cytotoxic T-lymphocyte antigen-4 (anti-CTLA-4) antibody (ipilimumab), anti-programmed death 1 (anti-PD-1) inhibitor (pembrolizumab, nivolumab, pidilizumab), anti-PD-L1 inhibitors (MPDL3280A, BMS-936559, MEDI4736), etc. (Table 1).

So far, passive immunotherapy has had limited success in the treatment of solid tumors, except in the treatment of malignant melanoma and renal cell cancer (RCC) [52-55]. The therapeutic options for advanced disease in RCC comprise of tyrosine-kinase inhibitors, m-TOR inhibitors, IL-2, antiangiogenic VEGF inhibitors, and IFNα. Spontaneous remissions and durable responses have been largely described as a result of this non-specific immune response. The prognosis of those patients unfortunately remains poor with a 5-year overall survival below 5% [56]. Thus, new options appear on the horizon involving the new specific targeted immunotherapies, focusing on the blockade of T cell regulation and functions, as well as activation of the dendritic cells (a form of active immunotherapy, described below). There are also phase I/II trials, studying the potential benefit of cellular adoptive immunotherapy using transfusion of stimulated patient's own T-lymphocytes. This adoptive T-lymphocyte therapy consists of infusion of ex vivo isolated, activated, or expanded tumor-specific T-lymphocytes [57]. There are different types of adoptive therapy, including TILs, engineered T-cells, expressing a specific cancer-related receptor (TCRs) or chimeric antigen receptor (CAR). Each of these approaches has its own advantages and disadvantages.

4.3. Immunotherapy as cancer prevention

Tumor cells express neoantigens that are expressed as a consequence of the malignant transformation of the host cell. The expression of neoantigens could also be the result of a

Target	Drug name	Biological description	Phase of the trial by tumor site		
			Phase I	Phase II	Phase III
CTLA-4	*Ipilimumab (BMS-734016)*	MAB	Pancreatic tumors	Ovarian Gastric	NSCLC CRPC
	Tremelimumab	MAB	MEL	MEL	-
PD-1	*Nivolumab (BMS-936558)*	Fully human IgG4 MAB	CRPC	Esophageal carcinoma	MEL, NSCLC
	Pembrolizumab Lambrolizumab (MK-3475)	Humanized IgG4 MAB	CRC, HCC, prostate cancer	RCC, CRC	MEL NSCLC RCC
	Pidilizumab (CT-011)	Humanized IgG1 MAB	-	MEL	-
	AMP-224	IgG1 fusion protein	Solid malignancies	-	-
PD-L1	*BMS-936559*	Fully human IgG4 MAB	NSCLC, MEL, CRC, RCC, ovarian, pancreatic, breast cancer	-	-
	MPDL3280A	MAB	NSCLC, MEL, CRC, ovarian, pancreatic, breast cancer	RCC, bladder carcinoma	NSCLC
	MEDI4736 Medimmune-AZ	IgG4 MAB	SCCHN	MEL	NSCLC

This is not an entirely comprehensive list of all trials that have been listed in www.clinicaltrials.com. (Source www.clinicaltrials.com)

Abbreviations:

CTLA-4: Cytotoxic T-lymphocyte-associated protein 4

PD-1: Programmed death 1

PD-L1: Programmed death 1 ligand

MAB: Monoclonal antibody

MEL: Melanoma

CRPC: Castrate-resistant prostate cancer

RCC: Renal cell carcinoma

NSCLC: Non-small cell lung cancer

CRC: Colorectal cancer

SCCHN: Squamous cell carcinoma of the head and neck

Table 1. Immune-checkpoint-pathway inhibitors and their targets in currently running clinical trials.

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viral or (more rarely) bacterial infection that induced and provoked this malignant transformation and thus the idea to vaccinate against those pathogens and prevent the associated cancer. More than 15% of all cancers are considered to be related to infectious agents [58]. Infection with human papilloma viruses (HPVs) is associated in about 30% of those cases (5% of all cancers) and hepatitis B and C viruses together with *Helicobacter pylori* (*H. Pylori*) account for 60% more of all infectious-agent-related cancers. It is logical that the success of conventional antimicrobial vaccines could encourage potential cancer vaccine prevention research. This approach has proven its efficacy in hepatitis B-induced hepatocellular carcinoma [59]. In carcinoma of the uterine cervix, it is a well-known fact that about 70% of them are caused by HPV types 16 and 18, and it is expected that HPV-vaccination could decrease the incidence not only of cervical cancer [60,61], but also of head-and-neck squamous cell carcinoma [62]. The mechanism, by which HPV induces malignant transformation, is by provoking the synthesis of two oncogene products, encoded by the virus, which degradate the tumor suppressor protein p53 and block other tumor suppressor proteins cells in the premalignant dysplasia cells, as well as the cell in the in situ and the invasive carcinomas. The recombinant vaccination against HPV leads to secretion of specific antibodies, protecting the non-infected organisms from HPV-infections, and the subsequent development of HPV-infection-related cancer sites [63]. No significant effect was demonstrated in already HPV-infected individuals [64].

4.4. Immunotherapy as anticancer treatment

There are 271 trials that are recruiting patients as assessed on 23 Apr 2015 at www.clinicaltrials.com. They include different DNA-vaccines, dendritic cell vaccines, peptide vaccines, allogeneic GM-CSF-secreting vaccines, recombinant vaccines, vaccines, targeting different auto-antigens as targets, etc. They are carried in patients with various solid malignancies, predominantly in melanoma, renal cell carcinoma, non-small cell carcinoma and other solid tumors. The immunotherapy approach was also implemented in the treatment of neuroendocrine tumors, e.g., vaccination with tumor lysate-pulsed DCs that induced a significant antitumor immune response in a neuroendocrine carcinoma of the pancreas [65].

A common example of the vaccine's use as treatment is the Bacillus Calmette-Guerin (BCG), which represents an attenuated mycobacterium, originally developed as anti-tuberculosis vaccine. It was only subsequently proven in 1976 that its immunostimulation characteristics led to antitumor effects in preventing recurrence in patients who underwent transurethral resection of superficial non-muscle invasive bladder carcinoma and carcinoma in situ when used as local repeated intravesical instillations [66]. Besides the non-specific immune activation, there is a theory suggesting that its anticancer effect might be attributed to specific BCG internalization in the tumor cells by the integrins and fibronectins of the tumor cells [67,68], provoking antigen-specific adaptive immune response as well [69-71].

A list of some of the more important clinical trials using cancer vaccines as therapeutic options are listed in Table 2.

Vaccine class	Name and target of the vaccine	Biological description	Phase of the trial by tumor site		
			Phase I	Phase II	Phase III
Tumor cell	Pancreatic tumor cell vaccine	GM-CSF gene-transfected tumor cell vaccine	MEL	Pancreas	
	Algenpantucel-L	Allogeneic human pancreatic cancer vaccine	RCC, prostate	MEL, NSCLC	Pancreas adenocarcinoma
	SL-701	Multivalent glioma-associated antigen vaccine	-	GBM	-
DC / APCs	Ovapuldencel-T	Autologous PBMCs in GM-CSF	-	Ovarian, peritoneal carcinoma	-
	AGS-003	Autologous DCs transfected with tumor and CD40L RNAs	-	-	RCC
	DCVAC/Pca	Autologous DCs pulsed with killed prostate cancer line LNCap	-	Prostate	Prostate
	DCVax-L	Autologous DCs pulsed with tumor lysate antigen	-	-	GBM
	CVac	Autologous DCs pulsed with MUC1-mannan fusion protein	-	Ovarian	-
	ICT-107	Autologous DCs pulsed with antigens	-	GBM	-
	MelCancerVac	Autologous DCs pulsed with allogeneic melanoma cell lysate	-	CRC, NSCLC	-
Peptides/ proteins	GV1001	hTERT peptide	MEL, pancreatic	HCC	NSCLC, pancreatic
	Nelipepimut-S	HER2/*neu* peptide combined with GM-CSF	-	-	Breast
	L-BLP25 (Tecemotide)	Liposome-encapsulated synthetic peptide derived from MUC-1	-	Rectal, NSCLC, prostate, CRC	NSCLC
	Rindopepimut	hEGFR variant III specific peptide conjugated to KLH	-	GBM	GBM
	POL-103A	Protein antigens from 3 melanoma cell lines with alum adjuvant	-	-	MEL
	IMA901	Synthetic vaccine consisting of 10 different TUMAPs	-	-	RCC
	MAGE-A3	MAGE-A3 combined with GM-CSF	-	Bladder	MEL
	MAGE-A3 ASCI	MAGE-A3 antigen-specific cancer immunotherapeutic	-	NSCLC	NSCLC

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Vaccine class	Name and target of the vaccine	Biological description	Phase of the trial by tumor site		
			Phase I	Phase II	Phase III
	Belange-pumatocel-L	Non-viral gene-based allogeneic tumor cell vaccine	-	NSCLC	NSCLC
	PVX-410	Multi-peptide vaccine	-	-	-
	IMA950	Multi-peptide glioma vaccine containing TUMAPs	GBM	GBM	-
	Racotumumab	Anti-idiotypic vaccine able to mimic the tumor-associated antigen NeuGcGM3	-	-	NSCLC
Genetic	Rilimogene galvacirepvec	Recombinant fowlpox/vaccinia virus encoding hPSA and TRICOM	Prostate	Prostate	Prostate
	CG0070	Oncolytic adenovirus encoding GM-CSF	-	Bladder	-
	TG4010	Recombinant modified vaccine virus strain Ankara, carrying coding sequences for human MUC1 antigen and human interleukin-2 and IL-2	Solid tumors	NSCLC	NSCLC

Abbreviations:

APC: Antigen-presenting cell

CRC: Colorectal cancer

DC: Dendritic cell

EGFR: Epidermal growth factor receptor

GBM: Glioblastoma

GM-CSF: Granulocyte-macrophage colony-stimulating factor

HCC: Hepatocellular carcinoma

hPSA: Human prostate specific antigen

hTERT: Human telomerase reverse transcriptase

IL-2: Interleukin-2

KLH: Keyhole limpet hemocyanin

MEL: Malignant melanoma

MUC1: Mucin 1

NSCLC: Non-small cell lung cancer

PBMC: Peripheral blood mononuclear cells

RCC: Renal cell carcinoma

TRICOM: Recombinant vaccinia virus vaccine encoding 3 co-stimulatory molecule transgenes B7.1, ICAM-1, and LFA-3

TUMAPs: Tumor-associated peptides

Table 2. Therapeutic use of cancer vaccines in clinical development in solid malignancies. This is not an entirely comprehensive list of all trials that have been listed in www.clinicaltrials.com. (Source www.clinicaltrials.com).

4.5. Predictive and prognostic biomarkers for immunotherapy

Research is ongoing in order to identify potential biomarkers for cancer immunotherapy. In order to optimize this process, we shall recently be in great demand of predictive/prognostic factors, justifying the selection of patients, who would be the best candidates for such novel, expensive, and potentially toxic treatments. PD-L1-positive cancers are associated with poorer prognoses than PD-1 negative. A correlation of PD-L1 expression and response rate was demonstrated in patients with the highest levels of PD-L1 expression and PD-L1-positive TILs [72]. The potential role of PD-L1 as well as TILs as a biomarkers remain to be elucidated.

The presence or absence of TILs also remains to be clarified. There are data that the immune system plays an important role in the process of recurrence of solid tumors. There is a multicenter study over 603 patients with colorectal cancer that showed the importance of the adaptive immune response and the presence/absence of T-lymphocytes in the resected tumor was a factor that correlated more accurately with clinical outcomes than the current parameters considered as gold standards for prognosis, histopathologically determined tumor stage (T) and nodal status (N), yielding a place for TILs as a potential prognostic marker in colorectal cancer [73] and potentially in other localizations of malignant tumors. It has also been proven for patients with large early-stage cervical cancer [74], muscle-invasive urothelial bladder carcinoma [75], and breast cancer [76]. All these findings suggest that assessment and consideration of the local intratumoral immune response in the primary tumor may have prognostic value and should be evaluated in the process of treatment decision taking.

5. Adverse effects of immunotherapy

Adverse events (AE) are graded using NCI Common Terminology Criteria for Adverse Events Version 4.0. Their management is important as the population of treated patients frequently consists of patients with disseminated disease or patients who have been previously treated with multiple treatment lines. Most frequent drug-related AEs with potential immune-related mechanism are hepatitis, pneumonitis, infusion reactions, colitis, arthralgia, and rash, necessitating sometimes the use of corticosteroids [77]. Fatigue, decreased appetite, nausea, dyspnea, diarrhea or constipation, vomiting, pyrexia, vitiligo, and headache are also described as immune-related AEs.

6. Classic chemotherapy and rationale for combination with immunotherapy

Introduction of immunotherapy into the classic chemotherapy regimens is undoubtedly a challenge. The use of chemotherapy aims complete direct cancer cell eradication, which frequently is not achieved. Post chemotherapy exposure to a tumor cell death may be induced, leading to cancer antigen release. These antigens could be subsequently processed by the APCs

http://dx.doi.org/10.5772/61211

and the cytotoxic CTLs. Besides a direct cytotoxic effect, such immune modulating effects have been proven for gemcitabine [78,79]; induction of immunogenic cancer cell death or immune sensitization for T-lymphocytes killing of the cancer cell has also been described for platinum compounds [29,80,81]. The effector cells of the immune system seem to remain unaffected [82], thus suggesting a possible rationale for searching of increased synergistic antitumor activity by combination of chemotherapy agents and immunotherapy. A large number of clinical trials are already running in multitude of solid tumor localizations. An example of a combination with chemotherapeutic agent is the emtansine/trastuzumab complex that is used in the treatment of HER-2 positive metastatic breast cancer.

Synergistic combinations with immunotherapy are also possible with radiotherapy [83], targeted agents [84], antiangiogenic drugs, or combining two immunotherapeutic agents with complementary mechanism of action [85]. There are multiple phase I–III trials, recruiting patients with solid tumors (MEL, NSCLC, RCC, CRC, etc.) where combinations of two immune checkpoint inhibitors are used in combination, e.g., anti-CTLA-4 MAB (ipilimumab) with PD-1 or PD-L1 inhibitors. CTLA-4 inhibitors stimulate the T cell activation in lymphatic tissues and increase the frequency of tumor-specific T cells, while the inhibition of the PD-1/PD-L1 axis modulates the T cell effector phase in order to overcome T cell anergy present in the tumor microenvironment [86].

A theory hypothesizes that combining immunotherapy with targeted agents could be synergistic as targeted agents promote apoptosis in tumor cells, thus enhancing tumor antigen presentation without adversely effecting immune effector cells; they can also directly modulate the immune response and improve immune-cell function, essentially acting as immune-sensitizing agents through different mechanisms [84]. The combination of immunotherapy with anti-angiogenic agents (e.g., *bevacizumab*, *sunitinib*, or *pazopanib*) is also supported by a strong biologic rationale as it has been shown that *bevacizumab* increases the maturation of DCs and antigen presentation process while *sunitinib* decreases the number of MDSCs and Tregs in the tumor microenvironment [87].

The rationale behind combination with radiotherapy is multidimensional, including radiation-induced tumor cell damage, leading to the spill of tumor-associated antigens, attracting the immune effector cells [80,88]. Radiotherapy also sensitizes the tumor cells, thus making them more susceptible to immune-mediated killing; it is partially due to the expression of MHC class I and death receptors [88]. There is a phase II trial in metastatic malignant melanoma (NCT01689974), which compares the use of ipilimumab as monotherapy or in combination with radiotherapy. Another important issue to be addressed in order to optimize the effect of this strategy is related to the timing of radiotherapy related to the administration of the immunotherapy [89].

The combination of agents always upfronts the question of antitumor effects and potential additive toxicity that is largely considered today. Currently, the most frequent combination remains the administration of immune adjuvants, e.g., IL-2 or GM-CSF with MAB or cancer vaccines, in order to stimulate the recruitment/activation of immune effector cells.

7. Tumor response evaluation of immunotherapy

An issue that has been recently recognized is the measurement of antitumor effect of immunotherapy. The cytotoxicity of chemotherapeutic agents often produces a measurable change in the size of the target lesions within weeks of the initial administration. Response for solid tumors is most frequently assessed using WHO or RECIST criteria [90,91]. For cytotoxic agents, these guidelines assume that an early increase in tumor growth and/or appearance of new lesions signal progressive disease (PD) and the term "progression" became synonymous with drug failure. Cessation of the currently used chemotherapy is thus recommended once PD has been detected.

On the other hand, immunotherapeutic agents enhance antitumor immune responses [92] and achievement of stable disease (SD) may also be viewed as an indicator of meaningful therapeutic effect. Beyond that, additional novel response patterns, observed with these agents, raise concerns about the interpretation and characterization of WHO or RECIST criteria. In studies with cytokines, cancer vaccines, and monoclonal antibodies, response classified as CR, PR, or SD has been shown to occur after an initial increase in tumor burden characterized as PD by WHO or RECIST criteria [93-96]. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because PD (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Thus, in order to systematically characterize additional patterns of response in patients treated with immunotherapy, underlying WHO criteria were evolved into immune-related response criteria (irRC) [97]. The core novelty of the irRC is the incorporation of measurable new lesions into "total tumor burden" and comparison of this variable to baseline measurements (before and after WHO PD, but not after confirmed irPD). Clinical activity often appears to be delayed following immunotherapeutic treatment and a period of apparent progression (as defined by the existing response criteria) may occur, followed by response. Four types of distinct response patterns have been described (two conventional and two new, unique to immunotherapy): 1) immediate response; 2) durable stable disease; 3) response after tumor burden increase; and 4) response in the presence of new lesions. The apparent increase in tumor burden that sometimes precedes response in patients receiving immune therapy may reflect either continued tumor growth until a sufficient immune response develops or transient immune-cell infiltration into the tumor with or without edema [97].

The use of irRC for response evaluation with immunotherapeutic treatment is considered clinically meaningful as they appear to be related to favorable survival. However, they are still in early development and prospective trials need to evaluate their role and potential association with survival.

8. Conclusion

A lot of scientific evidence has been recently accumulated over the role of the immune system in the prevention, development and progression of solid tumors. All this knowledge is

http://dx.doi.org/10.5772/61211

continuously enriched in order to implicate it into meaningful clinically relevant therapeutic strategies and use immunotherapy either alone or in combination with other systemic anticancer treatments. These new strategies will hopefully lead to improvement of the outcomes of patients with solid malignancies.

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